## REMARKS

Applicant's attorney wishes to thank the Examiner for the careful consideration given to the present application. Currently, claims 1-4 and 8-28 are pending, claims 10-27 have been withdrawn and claims 5-7 have been cancelled and new claim 28 has been added. Support for claim 28 may be found at, for example, paragraph [0015]. Applicant addresses each of the rejections set forth in the Office Action in the order presented therein.

35 U.S.C. § 112, first paragraph

Claims 5-7 are rejected under 35 U.S.C. § 112, first paragraph as allegedly being non-enabled. While Applicant respectfully disagrees, in order to expedite prosecution of the current application, Applicant has canceled claims 5-7, thereby rendering this rejection moot.

35 U.S.C. § 112, second paragraph

Claims 1-8 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite in the use of the recitation "asymmetric disulfide or the derivative thereof." While Applicant respectfully disagrees, in order to expedite prosecution of the current application, Applicant has amended claim 1 to recite "asymmetric disulfide or pharmaceutically acceptable salt thereof." Support for this amendment may be found at, for example, paragraphs [0054] and [0081] of the specification, which clearly describes exemplary pharmaceutically acceptable salts of asymmetric disulfides. In light of the amendment, Applicant respectfully requests that this rejection be withdrawn.

Claim 3 is further rejected as being indefinite for insufficient antecedent basis for the limitation "said hydrophilic polymer." Applicant has amended claim 3 to depend from new claim 28, which specifies that the polymer is a hydrophilic polymer, thereby providing sufficient antecedent basis for this limitation. Accordingly, this rejection should be withdrawn.

35 U.S.C. § 103

Claims 1-2 and 4-9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Powis et al., Anti-Cancer Drugs 1996, 7(3), pages 121-126 (hereinafter referred to as "Powis") in view of Halperin et al, U.S. Patent No. 5,633,274 (hereinafter referred to as "Halperin"). Applicant respectfully disagrees.

It is respectfully submitted that Powis in view of Halperin fails to render claims 1-2 and 4-9 directed to a sustained release delivery composition comprising an asymmetric disulfide and a matrix including at least one polymer obvious because neither reference alone or in combination provides any evidence that a composition comprising an asymmetric disulfide and a matrix including at least one polymer could be formulated to provide the sustained release delivery of an asymmetric disulfide. The references fail to even disclose or suggest a sustained release composition of an asymmetric disulfide. As set forth in *KSR Intn'l Co. v. Teleflex Inc.*, "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield *predictable results*." 127 S. Ct. 1727, 1731 (U.S. 2007) (emphasis added). As acknowledged in the present Office Action, the nature of the art of pharmaceuticals and their delivery is highly *unpredictable*. The Office has provided no evidence that one ordinarily skilled in the art would recognize that the sustained release delivery systems disclosed in Halperin for imidazoles would be suitable for asymmetric disulfides disclosed in Powis. There is no structural relationship between the imidazoles of Halperin and the asymmetric disulfides of the present claims. Notably, Halperin fails to even disclose an example of an imidazole in a sustained release delivery system, and obviously fails to disclose an example of an imidazole in a sustained release delivery system that contains a polymer matrix. Accordingly without a specific teaching that asymmetric disulfides could be formulated into a sustained release delivery composition, there is no reasonable expectation of success in view of the highly unpredictable nature of the art.

Additionally, as expressly set forth in the specification, the sustained delivery of asymmetric disulfides resulted in an unexpectedly increased and prolonged decrease in thioredoxin levels. Specifically, Applicant has provided evidence comparing the level and length of inhibition of thioredoxin levels following (i) a 1 hour infusion of 1-methylpropyl 2-imidazolyl disulfide (also referred to as PX-12) and (ii) a sustained 3 hour infusion of 1-methylpropyl 2-imidazolyl disulfide. As shown in Figure 3, when the infusion length was increased to 3 hours (from 1 hour as shown in Figure 2), the thioredoxin levels were constantly decreased at significantly lower levels and these decreased thioredoxin levels were consistently maintained for a significantly longer period of time. Such greater than expected results are evidence of the nonobviousness of the present claims. *See* MPEP 716.02(a). While Applicant can provide an affidavit to further explain and evidence such nonobviousness, it is respectfully submitted that

the specification provides more than sufficient evidence of nonobviousness and may be relied upon without the need of a declaration. *See* MPEP 716.02(b). In addition, it is respectfully submitted that the sustained delivery of asymmetric disulfides resulted in an unexpected improvement of adverse aspects, particularly a malodor, that were observed in clinical trials during the administration a non-sustained delivery asymmetric disulfide to patients. Accordingly, for the foregoing reasons, this rejection should be withdrawn.

Claims 1-2 and 4-9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Oblong et al., Cancer Chemother. Pharmacol. 1994, 34: 434-438 (hereinafter referred to as "Oblong") in view of Halperin. Applicant respectfully disagrees. It is respectfully submitted that for the reasons set forth above, namely the unpredictable nature of the present claims and the unexpected results specifically disclosed by Applicant, claims 1-2 and 4-9 are not obvious over Oblong in view of Halperin and this rejection should be withdrawn.

Claim 3 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Powis or Oblong in view of Royer, U.S. Patent No. 5,783,214 (hereinafter referred to as "Royer"). Applicant respectfully disagrees.

It is respectfully submitted that Powis or Oblong in view of Royer fails to render claim 3 directed to a sustained release delivery composition comprising an asymmetric disulfide and a matrix including at least one hydrophilic polymer obvious because neither reference alone or in combination provides any evidence that a composition comprising an asymmetric disulfide and a matrix including at least one hydrophilic polymer could be formulated to provide the sustained release delivery of an asymmetric disulfide. The references fail to even disclose or suggest a sustained release composition of an asymmetric disulfide with a hydrophilic polymer. As set forth in *KSR Intn'l Co. v. Teleflex Inc.*, "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield *predictable results*." 127 S. Ct. 1727, 1731 (U.S. 2007) (emphasis added). As acknowledged in the present Office Action, the nature of the art of pharmaceuticals and their delivery is highly *unpredictable*. Further, as noted by Royer, delivery systems of medicinal agents is a challenge because, among other things, the medicinal may be chemically modified during formulation. The delivery systems of Royer are specifically designed for the delivery of proteins, and there is no teaching or suggestion that the delivery of proteins using the systems of Royer could be applied to

asymmetric disulfides. The Office has provided no evidence that one ordinarily skilled in the art would recognize that the sustained release delivery systems disclosed in Royer for proteins would be suitable for asymmetric disulfides disclosed in Powis and Oblong. There is no structural relationship between the proteins of Royer and the asymmetric disulfides of the present claims and the disclosure of "anticancer drugs" in Royer is a genus of compounds that have no structural relationship and merely provide a functional property. Accordingly without a specific teaching that asymmetric disulfides could be formulated into a sustained release delivery composition, there is no reasonable expectation of success in view of the highly unpredictable nature of the art.

Additionally, as set forth above, Applicant has provided more than sufficient evidence of the unexpected results of a sustained release delivery of asymmetric disulfides. Accordingly, claim 3 is not obvious over Powis or Oblong in view of Royer, and this rejection should be withdrawn.

Claims 1-2, 4-7 and 9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kirkpatrick et al. Eur. J. Med. Chem. 1992, 27, pages 33-37 (hereinafter referred to as "Kirkpatrick") in view of Halperin. Applicant respectfully disagrees. It is respectfully submitted that for the reasons set forth above, namely the unpredictable nature of the present claims and the unexpected results specifically disclosed by Applicant, claims 1-2, 4-7 and 9 are not obvious over Kirkpatrick in view of Halperin and this rejection should be withdrawn.

Obviousness-Type Double Patenting

Claims 1-9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 49, 52-60, 63-69 and 71 of co-pending U.S. Application No. 10/366,751. Claims 1-9 are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-10 of co-pending U.S. Application No. 10/600,957. Applicant respectfully disagrees. As set forth above, Applicant has shown unexpected results in inhibiting thioredoxin levels for the sustained delivery of asymmetric disulfides in the specification, which evidences the nonobviousness of the current claims in light of the cited references. Accordingly, this rejection should be withdrawn.

## CONCLUSION

Applicant has timely filed this response. In the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Should the Examiner have any questions or comments, or need any additional information from Applicant's attorney, he is invited to contact the undersigned at his convenience.

Respectfully submitted,

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